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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,628	02/09/2006	Charli Kruse	B1180/20049	8428

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

NOTIFICATION DATE	DELIVERY MODE
10/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/561,628	KRUSE ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *18-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/06, 12/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 7/11/08 to claims 1, 3, 4, 6, 7, and 9-17 have been entered. No claims have been cancelled or added in this reply. Claims 1-41 remain pending in the current application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-17, in the reply filed on 7/11/08 is acknowledged. The traversal is on the ground(s) that examining all 3 inventions would not be burdensome on the examiner (Reply, page 6). This is not found persuasive because burden is not a consideration in a finding of lack of unity. Because this case was filed under 35 U.S.C. § 371, the guidelines for restriction are those provided in M.P.E.P. § 1850 and PCT Rules 13.1 and 13.2, inter alia. Applicant's citing of M.P.E.P. § 803 is improper, since chapter 800 applies only to those applications filed under 35 U.S.C. § 111(a). See M.P.E.P. § 801. Applicant has provided no convincing argument that the three inventions are unified by a special technical feature. The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species "treatment with immobilized endocrine growth factors" in the reply filed on 7/11/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse.

Claims 18-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/11/08.

Examination on the merits will commence at this time on claims 1-17 ONLY, to the extent they read on the elected species where applicable.

Specification

The disclosure is objected to because of the following informalities: At page 1, lines 27-29, the specification refers to claim numbers. Since claims are generally amended during prosecution (as claim 1 has been in the 7/11/08 reply) and may be canceled, these references do not clearly refer to any particular methods or product. If this paragraph is intended to refer to the original claims, the text of those claims should be placed into the specification such that the paragraph's meaning is clear. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co.*, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See M.P.E.P. § 2163.02. In this case, the skilled artisan would not have reasonably concluded at the time of the invention that applicant was in possession of the entire invention as claimed.

The independent claim is drawn to a method for generating cells producing pancreatic hormone by obtaining pluripotent stem cells from exocrine glandular tissue and then cultivating said stem cells to yield cells that produce pancreatic hormone. In some dependent claims, the manner of stimulation is further described (however, see the rejections below under 35 U.S.C. § 112, second paragraph). In some dependent claims, the source of the stem cells is more particularly pointed out.

By definition, a stem cell has two properties: it can produce differentiated progeny, and it can renew itself (see Potten et al., 2004, *Apoptosis: The Life and Death of Cells*, at pages 120-121; reference U). A pluripotent stem cell can differentiate into many different cell types (see MedlinePlus definition from http://www.nlm.nih.gov/medlineplus/mplusdictionary.html at reference V). Therefore, for a cell to be considered a "pluripotential stem cell," evidence must show that it can give rise to at least two different mature cell types and that it is self-renewing. Such evidence is lacking in this application.

It is noted that at page 2, line 5, of the specification, the cells giving rise to pancreatic hormone-producing cells are characterized as "pluripotent" and "stem cells." The working examples, however, provide insufficient evidence that the skilled artisan would have concluded that at the time of the invention, applicants possessed pluripotent stem cells obtained from exocrine tissue that give rise to pancreatic hormone-producing cells. In Example 1, whole rat pancreatic tissue is processed to give a single-cell suspension, which is in turn cultured in incubation medium. Example 2 details an experiment in which rat pancreatic acini are minced and digested to produce a single-

cell suspension. Example 3 teaches a method for producing a single-cell suspension of human parotid (salivary) gland tissue, and Example 4 teaches methods for culturing these parotid gland cells to yield organoid bodies. Examples 1-4 do not particularly indicate the end point of this culturing. Example 5 refers generally to methods for differentiating “stem cells”; however, Example 5 does not indicate which cells are being differentiated, and it does not indicate that the result is any particular type of mature cell. Examples 6-9 include few details (6) or appear to be prophetic (7-9). Example 10 discusses “insulin-producing cells that were obtained from the exocrine pancreas of a human being,” but this example includes no details about how the insulin-producing cells were made. None of the working examples clearly teaches that there are truly pluripotent stem cells in the exocrine tissue employed in the working examples. “Stem cells” are not the same as “progenitor cells" or “precursor cells.”

Claims 1-17 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in

the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The independent claim is drawn to a method for generating cells producing pancreatic hormone by obtaining pluripotent stem cells from exocrine glandular tissue and then cultivating said stem cells to yield cells that produce pancreatic hormone. In some dependent claims, the manner of stimulation is further described (however, see the rejections below under 35 U.S.C. § 112, second paragraph). In some dependent claims, the source of the stem cells is more particularly pointed out.

As discussed above in the written description rejection, the specification in view of the art fails to provide sufficient teachings that the skilled artisan would conclude that applicants possessed a method including obtaining *bona fide* pluripotent stem cells from exocrine tissue; therefore, the specification cannot enable methods of making pancreatic hormone-producing cells from exocrine tissue pluripotent stem cells. While the level of ordinary skill in this art is at the postdoctoral level, without a substantive teaching of the starting material, the method cannot be enabled.

Furthermore, even if the starting material were considered to be exocrine tissue (i.e., not necessarily stem cells), the specification in view of the art is insufficient to enable the claims across their entire scope. M.P.E.P. § 2164.03 reads, “The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*,

427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)…In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." The art of isolating pluripotent stem cells from exocrine tissue and transdifferentiating these cells to yield pancreatic hormone-producing cells (i.e., endocrine cells) must be considered "nascent," because a thorough search of the prior art found no such teachings at the time of the invention, so the amount of guidance required by applicant is relatively high.

Regarding claim 1, different types of pancreatic islets produce several different hormones, including insulin, glucagon, and somatostatin; Example 10 discusses "insulin-producing cells … obtained from the exocrine pancreas of a human," but the specification provides no teachings for producing cells that produce any pancreatic hormone other than insulin (i.e., beta-islet-like cells). The specification also includes no

clear evidence that any exocrine tissue other than pancreatic exocrine tissue can yield pancreatic hormone-producing cells. Examples 1-4 do not clearly indicate that the culturing steps discussed therein give rise to such cells.

Regarding claims 6 and 7, the specification includes only prophetic examples (e.g., Example 8) in which the alleged pluripotent stem cells are stimulated by fixed differentiation molecules. Example 9 may improperly incorporate essential material by reference; furthermore, this example appears to be prophetic. Given the nascent state of the art, these prophetic examples cannot enable each and every embodiment recited in claims 6 and 7. Indeed, there are no working examples in which a particular growth factor is immobilized and then contacted with pluripotent stem cells, and there is no evidence that any relevant genes are expressed in response to the culturing steps.

Finally, only rat and human glandular tissue is employed in the working examples; there is no evidence that any tissue from an invertebrate could be used as the starting material for obtaining the pluripotent stem cells.

While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 requires obtaining pluripotent stem cells that “have a capacity to form organoid bodies,” which is confusing for several reasons. First, especially in light of the dependent claims, it is not clear whether claim 1 requires that organoid bodies be formed or simply that the cells obtained have the ability to form the same. Second, the term "organoid bodies" is not clearly defined in the specification. Page 2, line 26, through page 3, line 15, discusses organoid bodies and appears to describe them simply as cell aggregates. If these bodies have specific properties that are material to patentability, the claim should reflect such. Clarification is required.

Because claims 2-17 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 2 requires that “stem cells isolated primarily from the organism" be cultured, but it is not clear whether this claim attempts to further limit the cells of claim 1 or requires that a second population of stem cells be cultured. The phrase “isolated primarily” is queried, since it indicates that some of these cells are isolated from the organism of claim 1 and some from another organism; the examiner suspects applicant means to require that the cells be primary cells, i.e. isolated directly from the organism. Clarification is required.

Claim 4 is confusing because, as discussed above, claim 1 does not require that the cells actually form organoid bodies, only that they have the potential to do so. Clarification is required.

The language in claim 5, specifically “stem cells isolated secondarily," is queried. Again, it is not clear whether this claim attempts to describe the stem cells of claim 1 or to require that an additional stem cell population be cultured. Clarification is required.

Claim 6 is extremely wordy; it is not clear what active method steps this claim is intended to require. Claim 1 requires the differentiation of stem cells to cells that produce pancreatic hormone; it is not clear how the “stimulating the generating" of these cells in claim 6 is related to the method. Clarification is required.

Claim 8 refers to "cellular imprinting,” which is queried. Generally, in cell biology, “imprinting” refers to epigenetic gene control in which certain nucleotides in a cell’s DNA are modified, e.g. with a methyl group. The term “imprinting” is discussed at page 3, line 27, et seq. in general and confusing terms. “Imprinting” appears to be synonymous with “treatment with growth and differentiation factors.” Applicant fails to provide a sufficiently limiting definition as to allow this non-art term to be used in the claims. Clarification is required.

Claim 13 refers to “secretory glands," which is confusing since by definition, glands secrete bioactive agents. Clarification is required.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP

714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651